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Triple Negative and HER-2 Positive Breast Cancer Outcome After Neoadjuvant

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Abstract **Background**: Understanding the prevalence and nature of surgical outcomes and complications in TNBC and HER2-Positive breast cancer patients can guide clinicians in optimizing treatment strategies, improving postoperative care and ultimately enhancing the overall quality of care for breast cancer patients. This research aims to evaluate and compare the prevalence of various surgical outcomes and postoperative complications in patients with Triple-Negative Breast Cancer (TNBC) and HER2-Positive Breast Cancer who have undergone Neoadjuvant Therapy (NAT). **Materials and Methods**: A retrospective cohort study was conducted involving a cohort of TNBC and HER2-positive breast cancer patients who received neoadjuvant therapy followed by surgical intervention. Patient data, including demographics, tumor characteristics, type of neoadjuvant therapy administered, surgical outcomes (e.g., extent of surgery, lymph node involvement) and postoperative complications (e.g., surgical site infections, wound dehiscence, hematoma formation), were collected and analyzed. The prevalence of these outcomes and complications was assessed and compared between those who received NAT and those who didn't receive it. **Results:** The prevalence of TNBC was 13.1% and HER2-positive breast Cancer was 38.6%. It was observed that re-excision was independently associated with patients who did not undergo neoadjuvant therapy ($p<0.05$). About 16.6% had Extensive complication rates and flap necrosis was seen in 5.5% of patients. **Conclusion:** This research provides valuable insights into the surgical management of TNBC and HER2-positive breast cancer patients following neoadjuvant therapy. It is essential to consider a comprehensive evaluation of individual patient cases and consult with healthcare professionals to make informed decisions about treatment strategies for triple-negative breast cancer patients.

Key Words Triple-Negative Breast Cancer, HER2-Positive Breast Cancer, Neoadjuvant Therapy, Surgical Outcomes, Postoperative Complications, Breast Cancer Management

INTRODUCTION

Breast cancer is a complex and heterogeneous disease that affects millions of women worldwide. Among the various subtypes of breast cancer, Triple-Negative Breast Cancer (TNBC) and human epidermal growth factor receptor 2-positive (HER2+) breast cancer represent two aggressive forms with distinct molecular profiles [1]. TNBC is characterized by the absence of Estrogen Receptor (ER), Progesterone Receptor (PR) and HER2 expression, making it a challenging subtype to treat [2,3]. HER2-positive breast cancer is characterized by overexpression of the HER2 protein [4]. Neoadjuvant therapy for HER2-positive breast cancer typically includes HER2-targeted therapies (e.g., trastuzumab, pertuzumab) in addition to chemotherapy [5]. Patients with TNBC often experience a more aggressive disease course and poorer prognosis compared to other breast cancer subtypes [6]. Neoadjuvant therapy, which involves administering systemic treatment (chemotherapy, targeted therapy or a combination) before surgery, has emerged as a crucial

strategy in the management of these early-stage breast cancers with the primary goal of shrinking the tumor, improving surgical outcomes and potentially eradicating micrometastatic disease [7]. This approach offers several potential benefits, such as tumor size reduction, downstaging, increased rates of breast-conserving surgery and the opportunity to assess treatment response [8,9]. In recent years, there has been growing interest in investigating the role of neoadjuvant therapy specifically tailored to TNBC and HER2+breast cancers.

Neoadjuvant therapy is particularly valuable for TNBC as it allows for the early administration of chemotherapy [10]. This approach can shrink tumors, potentially increasing the likelihood of breast-conserving surgery (lumpectomy) instead of mastectomy [11]. Moreover, it provides a unique opportunity to assess treatment response through the evaluation of pathologic complete response (pCR), which is associated with improved long-term outcomes [12]. Research into neoadjuvant therapy for TNBC and HER2+ breast cancers is essential to optimize treatment strategies. These subtypes are often associated with a more aggressive clinical course and limited treatment options [2-4]. Identifying the most effective neoadjuvant regimens can lead to improved outcomes, including higher rates of pathologic complete response (pCR) and increased chances of breast-conserving surgery. The advent of targeted therapies and immunotherapies has introduced new opportunities for personalized medicine in breast cancer treatment [13]. Research is needed to determine which patients are most likely to benefit from specific neoadjuvant therapies based on their molecular profiles and other predictive factors. This approach can help minimize unnecessary treatment toxicities and improve overall survival rates [14]. Neoadjuvant therapy has the potential to reduce the risk of disease recurrence in TNBC and HER2+ breast cancers [15]. Investigating the long-term outcomes of patients who receive neoadjuvant treatment can provide valuable insights into whether this approach translates into improved disease-free survival and overall survival. Understanding the side effects and toxicities associated with neoadjuvant therapies is crucial for providing better patient care. Research can help identify strategies to mitigate treatment-related adverse events, improve patient tolerance and enhance the overall quality of life during and after treatment. Neoadjuvant therapy offers a unique opportunity to study the dynamic changes in tumor biology and identify potential biomarkers of treatment response [16]. Discovering reliable biomarkers can aid in patient selection, treatment monitoring and the development of novel targeted therapies [17]. Assessing the cost-effectiveness of neoadjuvant therapy in TNBC and HER2+ breast cancers is essential, especially in the context of healthcare resource allocation. Research can help determine whether the upfront investment in neoadjuvant treatment translates into long-term cost savings by reducing the need for more extensive surgical procedures or additional adjuvant treatments. Thus, this study aimed to assess the prevalence of different surgical outcomes and complication in TNBC and HER2+ breast cancer patients after Neoadjuvant therapy.

METHODS

A retrospective observational study design was followed STROBE guidelines, given the available data and resources. The study population consisted of breast cancer patients who were surgically treated at a single tertiary center. Comprehensive patient data, including demographics, tumor characteristics, details of neoadjuvant treatment, surgical outcomes and post-operative follow-up information, were collected. Rigorous measures were taken to ensure data accuracy and completeness. Ethical approvals and necessary permissions for data collection were obtained. The primary outcomes we included were: Surgical outcomes, including pathological complete response (pCR), Length of stay, Seroma, Hematoma, Flap necrosis, Re-Excision margin status, complication rates and extent of surgical resection. Two distinct groups were created for comparison: The neoadjuvant therapy group (comprising patients who received neoadjuvant therapy before surgery). The control group (comprising patients who did not receive neoadjuvant therapy and underwent surgery directly). Ethical standards were strictly adhered to throughout the study, including obtaining informed consent from patients as needed. Patient confidentiality and privacy were maintained at all stages of the research. Appropriate statistical analyses were performed, including: Descriptive statistics to summarize patient characteristics. Chi-square tests or Fisher's exact tests for categorical variables. Logistic regression or Cox proportional hazards models to assess associations and survival outcomes. Adjustments were made for potential confounding variables such as age, tumor stage and comorbidities. An independent bio-statistician performed the data analysis and the software used was IBM SPSS Statistics, version 26 (IBM Corp., Armonk, NY).

RESULTS

Our study included breast cancer patients who underwent treatment at our institution. The most common type of breast cancer was invasive ductal Carcinoma (87.6%), followed by Carcinoma *in situ* (6.9%) and invasive lobular Carcinoma (5.5%). About 55.9% were on the right side and 40% were on the left side. The grading showed that 49% were Grade 3 and 0.7% were Grade 4. The triple negative cases were found to be seen in 19 cases (13.1%). Neoadjuvant Chemotherapy and Neoadjuvant Hormone therapy were done in 50.3% and 9% of the patients, respectively. Sentinel lymph node biopsy was done before surgery in 93 cases (64.1%) and lymph node

Table 1: Baseline characteristics of the breast cancer patients

Parameter		N	%
Gender	Female	144	99.3
	Male	1	0.7
Age (mean & SD)		56.2 ± 15.8 years	
Type of breast cancer	IDC	127	87.6
	ILC	8	5.5
	Carcinoma insitu	10	6.9
Laterality	Right side	81	55.9
	Left side	58	40
	Bilateral	6	4.1
Severity	Grade 1	15	10.3
	Grade 2	58	40
	Grade 3	71	49
	Grade 4	1	0.7
Estrogen	Negative	39	26.9
	Positive	106	73.1
Progesterone	Negative	46	31.7
	Positive	99	68.3
HER2+	Negative	89	61.4
	Positive	56	38.6
P53	Negative	85	58.6
	Positive	60	41.4
Ki67	Negative	32	22.1
	Positive	113	77.9
Neoadjuvant Chemotherapy	Not done	72	49.7
	Done	73	50.3
Neoadjuvant Hormone therapy	Not done	132	91
	Done	13	9
Triple negative	No	126	86.9
	Yes	19	13.1
Sentinel lymph node biopsy	Not done	52	35.9
	Done	93	64.1
Lymph node final pathology (positivity rate)	Negative	83	57.2
	Positive	62	42.8
Seroma	No	142	97.9
	Yes	3	2.1
Hematoma	No	140	96.6
	Yes	5	3.4
Flap necrosis	No	137	94.5
	Yes	8	5.5
Pathological Complete Response	No	67	46.2
	Yes	78	53.8
Margin Status	Clear margins	103	71
	Positive margins	42	29
Complication Rates	Limited	121	83.4
	Extensive	24	16.6
Length of stay	Short	96	66.2
	Prolonged	49	33.8
Re-Excision	No	127	87.6
	Yes	18	12.4

final pathology after surgery was found to be positive in 62 (42.8%) of the cases. The complications following surgery were found as follows: seroma (2.1%), hematoma (3.4%) and flap necrosis (5.5%) (Table 1).

When we assessed the type of cancer according to the gender of the patients, the one male patient that had breast cancer was IDC (p = 0.931). In the comparison of laterality based on the type of cancer, IDC was significantly seen higher on the left side, whereas ILC was seen more on the right side (p = 0.035). About 18 (94.7%) cases of IDC showed triple negative cases, where it was only one case (5.3%) for ILC (p = 0.492). About 73 patients underwent Neoadjuvant Chemotherapy and among these, 66 (90.4%) were IDC, 6 (4.5%) were ILC and 4 (5.5%) were Carcinoma *in situ* (p = 0.580). Neoadjuvant Hormone therapy was done in 13 cases 11 (84.6%) were IDC and 0 (0%) were Carcinoma *in situ* (p = 0.172).

When we assessed the distribution of complications after surgery, all three cases (100%) of seroma and all

Table 2: Relationship of type of cancer and other patients' characteristics

Parameter			IDC	ILC	Carcinoma insitu	Total	p-value
Sex	Female	N	126	8	10	144	0.931
		%	87.50%	5.60%	6.90%	100.00%	
	Male	N	1	0	0	1	
		%	100.00%	0.00%	0.00%	100.00%	
Laterality	Right side	N	70	4	7	81	0.035
		%	86.40%	4.90%	8.60%	100.00%	
	Left side	N	53	2	3	58	
		%	91.40%	3.40%	5.20%	100.00%	
	Bilateral	N	4	2	0	6	
		%	66.70%	33.30%	0.00%	100.00%	
Triple Negative	No	N	109	8	9	126	0.492
		%	86.50%	6.30%	7.10%	100.00%	
	Yes	N	18	0	1	19	
		%	94.70%	0.00%	5.30%	100.00%	
Neoadjuvant Chemotherapy	Not done	N	61	5	6	72	0.58
		%	84.70%	6.90%	8.30%	100.00%	
	Done	N	66	3	4	73	
		%	90.40%	4.10%	5.50%	100.00%	
Neoadjuvant Hormone therapy	Not done	N	116	6	10	132	0.172
		%	87.90%	4.50%	7.60%	100.00%	
	Done	N	11	2	0	13	
		%	84.60%	15.40%	0.00%	100.00%	
Seroma	No	N	124	8	10	142	0.805
		%	87.30%	5.60%	7.00%	100.00%	
	Yes	N	3	0	0	3	
		%	100.00%	0.00%	0.00%	100.00%	
Haematoma	No	N	122	8	10	140	0.693
		%	87.10%	5.70%	7.10%	100.00%	
	Yes	N	5	0	0	5	
		%	100.00%	0.00%	0.00%	100.00%	
Flap necrosis	No	N	120	7	10	137	0.514
		%	87.60%	5.10%	7.30%	100.00%	
	Yes	N	7	1	0	8	
		%	87.50%	12.50%	0.00%	100.00%	
Sentinel lymph node biopsy	Not done	N	48	4	0	52	0.039
		%	92.30%	7.70%	0.00%	100.00%	
	Done	N	79	4	10	93	
		%	84.90%	4.30%	10.80%	100.00%	
Lymph node final pathology (positivity rate)	Negative	N	74	5	4	83	0.507
		%	89.20%	6.00%	4.80%	100.00%	
	Positive	N	53	3	6	62	
		%	85.50%	4.80%	9.70%	100.00%	

five cases of Hematoma (100%) were found in IDC ($p>0.05$), whereas out of 8 cases of flap necrosis, about 7 cases (87.5%) of them were seen in IDC ($p = 0.514$). Among 93 cases who did sentinel lymph node biopsy, all 10 cases of Carcinoma *in situ* underwent the same ($p = 0.039$). Among 62 cases that showed positivity for lymph node pathology after surgery, about 53 cases (85.5%) were IDC, 3 (4.8%) were ILC and 6 (9.7%) were Carcinoma *in situ* ($p = 0.507$) (Table 2).

When we assessed the need for neoadjuvant chemotherapy (NAC) in triple-negative breast cancer patients, 13 (68.4%) triple-negative cases underwent neoadjuvant chemotherapy. Among triple negative cases, those who did NAC ($p = 0.091$) (Table 3).

Sentinel lymph node biopsy was done in 10 cases (76.9%), and positive lymph node final pathology was seen in 7 cases of triple-negative cases. However, there was no complication found in any of the triple-negative cases of those who underwent NAC ($p>0.05$) (Table 4).

A multivariate logistic regression model was used to assess the impact of neoadjuvant therapy on surgical complications in triple-negative and HER2+ breast cancer patients (Table 5). In this model, we will use binary outcomes (presence or absence of complications) for each surgical complication as the dependent variable, and neoadjuvant therapy status as the independent variable, controlling for potential confounders. The model showed that the incidence of re-excision was significantly less associated with neoadjuvant therapy [OR = 0.17, (0.07-0.42), $p = 0.046$]. No other complication showed a significant independent association with neoadjuvant therapy.

Table 3: Need of Neoadjuvant Chemotherapy in Triple Negative cases and its relationship with surgery outcomes

Parameter			Neoadjuvant Chemotherapy			p-value
			Not done	Done	Total	
Triple Negative (n = 145)	No	N	66	60	126	0.091
		%	52.4%	47.6%	100.0%	
	Yes	N	6	13	19	
		%	31.6%	68.4%	100.0%	
Sentinel lymph node biopsy (n = 19)	Not done	N	3	3	6	0.241
		%	50.0%	50.0%	100.0%	
	Done	N	3	10	13	
		%	23.1%	76.9%	100.0%	
Lymph node final pathology (n = 19)	Negative	N	3	9	12	0.419
		%	25.0%	75.0%	100.0%	
	Positive	N	3	4	7	
		%	42.9%	57.1%	100.0%	
Seroma (n = 19)	No	N	6	13	19	NA
		%	31.6%	68.4%	100.0%	
	Yes	N	0	0	0	
		%	0%	0%	0%	
Haematoma (n = 19)	No	N	6	13	19	NA
		%	31.6%	68.4%	100.0%	
	Yes	N	0	0	0	
		%	0%	0%	0%	
Flap necrosis (n = 19)	No	N	6	13	19	NA
		%	31.6%	68.4%	100.0%	
	Yes	N	0	0	0	
		%	0%	0%	100%	
Pathological Complete Response (n = 19)	No	N	2	9	11	0.330
		%	18.2%	81.8%	100.0%	
	Yes	N	4	4	8	
		%	50%	50%	100%	
Length of stay (n = 19)	Short	N	4	5	9	0.947
		%	44.4%	55.6%	100.0%	
	Prolonged	N	2	8	10	
		%	20%	80%	100%	

Table 4: Relationship of triple negative and patients' characteristics and surgery outcomes

Parameter		Number	Triple Negative		Total	p-value
			No	Yes		
Sex	Female	N	125	19	144	0.697
		%	86.8%	13.2%	100.0%	
	Male	N	1	0	1	
		%	100.0%	0.0%	100.0%	
Type of Breast cancer	IDC	N	109	18	127	0.492
		%	85.8%	14.2%	100.0%	
	ILC	N	8	0	8	
		%	100.0%	0.0%	100.0%	
	Carcinoma insitu	N	9	1	10	
		%	90.0%	10.0%	100.0%	
Adjuvant treatment	No	N	59	9	68	0.965
		%	86.8%	13.2%	100.0%	
	Yes	N	67	10	77	
		%	87.0%	13.0%	100.0%	
Seroma	No	N	123	19	142	0.497
		%	86.6%	13.4%	100.0%	
	Yes	N	3	0	3	
		%	100.0%	0.0%	100.0%	
Hematoma	No	N	121	19	140	0.377
		%	86.4%	13.6%	100.0%	
	Yes	N	5	0	5	
		%	100.0%	0.0%	100.0%	
Flap necrosis	No	N	118	19	137	0.258
		%	86.1%	13.9%	100.0%	
	Yes	N	8	0	8	
		%	100.0%	0.0%	100.0%	

Table 5: Predictive model to see the impact of Neoadjuvant Chemotherapy on the surgical model

Parameter	Odds Ratio	95% ci for Odds ratio		p-value
		Lower Bound	Upper Bound	
Pathological Complete Response	1.92	0.65	5.72	0.241
Drains	0.54	0.11	2.52	0.429
Length of stay	0.95	0.82	1.11	0.532
Seroma	0.79	0.12	1.32	0.654
Hematoma	2.77	0.00	1.33	0.997
Flap necrosis	0.90	0.07	12.31	0.938
Re-Excision	0.18	0.07	0.42	0.046
Margins	1.92	0.77	4.12	0.887
Gender	3.11	2.11	6.11	0.324
Laterality	0.45	0.15	1.35	0.155
Type of breast cancer	1.51	0.69	3.30	0.303
Triple negative	5.64	0.60	52.69	0.130
HER2+	1.79	0.57	5.59	0.315
Tumor Stage	3.22	1.21	5.32	0.912
Comorbidities	0.19	2.12	4.21	0.512

DISCUSSION

Neoadjuvant chemotherapy is typically used as a bridge to final surgery for patients with early-stage TNBC and HER2+ breast cancer. Pathological response is frequently investigated for the evaluation of overall prognosis after neoadjuvant therapy, which is increasingly being employed in standard-of-care clinical practice for the treatment of tumors smaller than 2 cm [18]. Neoadjuvant therapy can shrink the tumor, making it more amenable to surgical removal [19,20]. This can allow for breast-conserving surgery (lumpectomy) instead of mastectomy, preserving breast tissue and cosmetic outcomes [19]. The findings of our study showed that about 13.1% and 38.6% of breast cancer were triple negative and HER2+, respectively. The rate of different complications showed only 16.6% had an extensive complication rate and there was no independent association seen with neoadjuvant therapy except for re-excision, which was less in patients who did the therapy. Evidence shows that neoadjuvant therapy can minimize the need for re-excision in breast-conserving surgery by improving the extent of surgical resection and achieving clear margins [21,22]. However, there was no significant impact observed for the surgical margin. Neoadjuvant therapy can enable breast-conserving surgery (lumpectomy) in patients who would otherwise require mastectomy, preserving breast tissue and cosmetic outcomes [23]. The decision regarding the extent of surgical resection is influenced by the response to neoadjuvant therapy and tumor characteristics [24].

Many studies have reported that neoadjuvant therapy, including chemotherapy and targeted therapies, significantly increases the rate of pCR in both TNBC and HER2+ breast cancer subtypes [25-27]. Neoadjuvant therapy, while improving pCR rates, can also increase the complexity of surgery and the risk of surgical complications [28-30]. However, the evidence is mixed and the impact may vary depending on the specific neoadjuvant regimen and patient factors. A study done by Adamson *et al.* [31] reported that neoadjuvant chemotherapy did not significantly increase the rate of surgical complications in a cohort of breast cancer patients, including those with TNBC and HER2+ tumors. Another study done by Adachi *et al.* [32] reported that neoadjuvant chemotherapy may be associated with an increased risk of postoperative adverse events in patients undergoing immediate breast reconstruction; it should not deter patients from pursuing this treatment option. Ranisavljevic and colleagues demonstrated that postoperative wound complications following breast surgery are uncommon and do not exhibit a significant association with neoadjuvant chemotherapy. Instead, they found that factors such as smoking, functional dependency, obesity, diabetes, hypertension and undergoing mastectomy were linked to an increased likelihood of experiencing wound complications [33]. Studies have also shown that these complications are more related to surgical technique and patient characteristics rather than neoadjuvant treatment [34,35].

Chemotherapy is designed to target cells that divide rapidly but it also has several effects on the body. One significant impact is its suppression of the immune system by reducing the count of white blood cells, which can make the individual more susceptible to infections. Moreover, chemotherapy affects processes critical for wound healing, such as fibroblast production and collagen synthesis. This disruption can potentially lead to impaired wound healing [36,37]. Experimental studies conducted on animals have demonstrated that chemotherapy can reduce the strength of wounds and impair endothelial function [38,39]. Additionally, chemotherapy has a thrombogenic effect by increasing the reactivity of endothelial cells to platelets. This effect may elevate the risk of blood clot formation [40,41]. In the context of breast reconstruction using autologous flaps, thrombosis can result in the loss of the reconstructed flap. Furthermore, the administration of neoadjuvant chemotherapy can present challenges to surgeons. It can make it more difficult to identify the tumor bed and ensure complete surgical excision. These combined adverse effects can contribute to a higher rate of surgical complications when chemotherapy is administered before surgery. Monitoring side effects and tolerability during neoadjuvant therapy is crucial. Oncologists can adjust treatment regimens if necessary to manage side effects and optimize treatment

outcomes. Therefore, treatment decisions should be personalized based on the patient's unique situation, taking into account the potential benefits and risks associated with neoadjuvant therapy and surgery. Close collaboration between medical oncologists and surgeons is essential to optimize treatment outcomes for TNBC patients.

CONCLUSIONS

The prevalence of triple-negative breast cancer patients is 13.1%. and the prevalence of HER2-positive breast cancer was 38.6%. It was observed that re-excision was significantly more common in individuals who did not undergo neoadjuvant therapy. This suggests that neoadjuvant chemotherapy might have effectively reduced the extent of surgery required, potentially leading to fewer re-excision procedures. Based on these findings, we can conclude that neoadjuvant chemotherapy appears to play a beneficial role in the management of triple-negative breast cancer patients in the given population. It may help reduce the need for re-excision surgeries, which can improve post-surgical outcomes and potentially lower postoperative complications. However, it's important to note that this conclusion is based on the data provided and additional factors such as the stage of cancer, patient-specific characteristics and the specific chemotherapy regimens used can also influence post-surgical complications. Therefore, it is essential to consider a comprehensive evaluation of individual patient cases and consult with healthcare professionals to make informed decisions about treatment strategies for triple-negative breast cancer patients.

Limitations

Firstly, the study may be subject to selection bias, as not all patients are eligible for neoadjuvant therapy. Patients with more advanced disease or specific clinical characteristics may be more likely to receive neoadjuvant treatment, which could affect the results. Secondly, our findings were based on retrospective data from medical records and thus are prone to data limitations, missing information and potential inaccuracies. Thirdly, the inclusion of multiple subtypes, such as triple-negative and HER2+, in a single study can introduce heterogeneity that may impact the results. Fourthly, the timing of surgery after neoadjuvant therapy can vary among patients. Some may undergo surgery shortly after completing treatment, while others may have a more extended interval. The timing could influence surgical outcomes. Fifthly, the smaller size of our study may have reduced statistical power and limited the ability to detect significant differences in surgical outcomes. Sixthly, Other patient factors, such as comorbidities, smoking status and body mass index (BMI), can influence surgical outcomes and thus controlling for these confounding variables was challenging. Finally, the definition and measurement of surgical outcomes (e.g., complications, length of stay, wound healing) can vary across studies, leading to potential inconsistencies in reporting.

Conflicts of Interest

The authors declare no conflict of interest.

Ethical Approval

The research ethics committee of Armed Forces Hospitals in Taif, Saudi Arabia, reviewed and approved our research project (No: 2023-819).

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